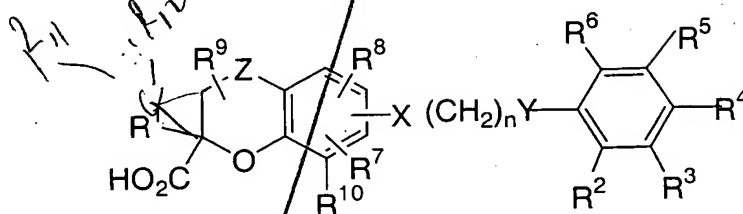


WHAT IS CLAIMED IS:

1. A compound having the formula I:



I

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Z is selected from the group consisting of CH₂ and C=O;

R¹ is selected from the group consisting of H, -OH, C₁-7alkyl, C₂-7alkenyl, C₂-7alkynyl, -OC₁-3alkyl, -OC₂-3alkenyl, -OC₂-3alkynyl, F, Br, Cl, and Ar, wherein alkyl, alkenyl, alkynyl, -Oalkyl, -Oalkenyl and -Oalkynyl are linear or branched and are optionally substituted with (a) 1-7 halogen atoms, (b) 1-3 groups independently selected from (i) -OC₁-3alkyl, which is optionally substituted with 1-5 halogen atoms, and (ii) phenyl, which is optionally substituted with 1-3 groups independently selected from halogen, C₁-5alkyl and -OC₁-3alkyl, said C₁-5alkyl and -OC₁-3alkyl being linear or branched and optionally substituted with 1-5 halogens, or (c) a mixture of (a) and (b); or alternatively,

R¹ is a group -CR¹¹R¹²- which bridges between the carbon to which R¹ is attached in Figure I and the adjacent carbon on the heterocyclic ring, yielding a cyclopropane ring;

R¹¹ and R¹² are independently selected from the group consisting of hydrogen, halogen, C₁-5alkyl, C₂-5alkenyl, C₂-5alkynyl, -OC₁-3alkyl, -OC₂-3alkenyl, -OC₂-3alkynyl, -CO₂H, -CO₂C₁-5alkyl, -CO₂C₂-5alkenyl, -CO₂C₂-5alkynyl, and phenyl, where alkyl, alkenyl, alkynyl, -Oalkyl, -Oalkenyl, -Oalkynyl, -CO₂alkyl, -CO₂alkenyl, and -CO₂alkynyl are linear or branched and are optionally substituted with (a) 1-5 halogens, (b) 1-3 substituents independently

selected from -OCH₃ and -OCF₃, or (c) a mixture thereof, and phenyl is optionally substituted with 1-3 groups independently selected from halogen, C₁-5alkyl, and -OC₁-3alkyl, wherein C₁-5alkyl and -OC₁-3alkyl are linear or branched and are optionally substituted with 1-5 halogens;

5

Ar is selected from the group consisting of Aryl, Hetcyc, Hetaryl, and Benzoheterocycle, wherein Aryl, Hetcyc, Hetaryl, and Benzoheterocycle are in each instance optionally substituted with 1-5 substituents independently selected from (a) halogen, (b) C₁-5alkyl, (c) C₂-5alkenyl, (d) C₂-5alkynyl, (e) -OC₁-5alkyl, (f) -OC₂-5alkenyl, (g) -OC₂-5alkynyl, (h) -SO_xC₁-5alkyl, (i) -SO_xNR^aR^b, (j) -SO_xphenyl, (k) -C(O)C₁-3alkyl, and (l) -C(O)NR^aR^b, wherein in each instance, each alkyl, alkenyl and alkynyl is linear or branched and is optionally substituted with (a) 1-5 halogen atoms, (b) 1-2 groups independently selected from -OC₁-3alkyl, which is linear or branched and is optionally substituted with 1-5 halogens, or (c) a mixture thereof, and wherein phenyl is optionally substituted with 1-3 substituents independently selected from halogen, C₁-3alkyl, and C₁-3alkoxy, wherein C₁-3alkyl and C₁-3alkoxy are linear or branched and are optionally substituted with 1-5 halogens, and wherein Hetcyc and Benzoheterocycle may each optionally have a C₃-6-spiro-cycloalkyl substituent on the ring on a carbon atom that can have gem-disubstitution, wherein the spiro-cycloalkyl group is optionally substituted with 1-2 groups independently selected from methyl, trifluoromethyl, methoxy, trifluoromethoxy and halogen;

15

x is selected from 0, 1 and 2;

25

Aryl is a carbocyclic 6-10 membered monocyclic or bicyclic aromatic ring system;

30

Hetcyc is a 5- or 6-membered saturated or partly saturated monocyclic heterocycle having 1-4 heteroatoms independently selected from N, S and O in the perimeter of the ring, wherein N may optionally be NR^a and S may optionally be SO or SO₂;

Hetaryl is a 5- or 6-membered heteroaromatic ring having 1-4 heteroatoms independently selected from O, S, and N in the perimeter of the ring, where N may optionally be NR^a , and S may optionally be SO or SO_2 ;

5 Benzoheterocycle comprises a 5 or 6-membered heterocyclic ring which may be saturated, partly unsaturated or aromatic, and a benzene ring, wherein said heterocyclic ring and said benzene ring are fused together, wherein said heterocyclic ring comprises 1-3 heteroatoms independently selected from O, S, and N in the perimeter of the ring, where N may optionally be NR^a , and S may optionally be
10 SO or SO_2 ;

15 R^a and R^b are independently selected from the group consisting of H, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, $-\text{C}(\text{O})\text{C}_{1-5}$ alkyl, $-\text{C}(\text{O})\text{C}_{2-5}$ alkenyl, $-\text{C}(\text{O})\text{C}_{2-5}$ alkynyl, $\text{SO}_x\text{C}_{1-5}$ alkyl, SO_x phenyl, $\text{SO}_x\text{NR}^d\text{R}^e$, $-\text{C}(\text{O})\text{NR}^d\text{R}^e$, halogen, and phenyl, wherein in all instances, alkyl, alkenyl, and alkynyl are linear or branched and are optionally substituted with (a) 1-5 halogen atoms, (b) 1-3 groups independently selected from $-\text{OCH}_3$, $-\text{OCF}_3$ and phenyl, or (c) a mixture thereof, wherein phenyl in all occurrences is optionally substituted with 1-3 substituents independently selected from halogen, C_{1-3} alkyl, and C_{1-3} alkoxy, said C_{1-3} alkyl and
20 C_{1-3} alkoxy being linear or branched and optionally substituted with 1-5 halogens;

25 R^d and R^e are independently selected from H, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, and phenyl, wherein said alkyl, alkenyl, and alkynyl are linear or branched and are optionally substituted with (a) 1-5 halogen atoms, (b) 1-3 groups independently selected from $-\text{OCH}_3$, $-\text{OCF}_3$ and phenyl, or (c) a mixture thereof, wherein phenyl in all occurrences is optionally substituted with 1-3 substituents independently selected from halogen, C_{1-3} alkyl, and C_{1-3} alkoxy, said C_{1-3} alkyl and C_{1-3} alkoxy being linear or branched and optionally substituted with 1-5 halogens;

30 X and Y are independently selected from the group consisting of O, S, SO, SO_2 , NR^a and CH_2 ;

n is an integer from 1-6;

O, S, N, C

5 R², R³, R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are independently selected from the group consisting of H, halogen, C₁₋₇alkyl, C₂₋₇alkenyl, C₂₋₇alkynyl, -OH, -OC₁₋₅alkyl, -OC₂₋₅alkenyl, -OC₂₋₅alkynyl, -C(O)C₁₋₅alkyl, -C(O)C₂₋₅alkenyl, -C(O)C₂₋₅alkynyl, -C(O)OC₁₋₅alkyl, -C(O)OC₂₋₅alkenyl, -C(O)OC₂₋₅alkynyl, -OC(O)C₁₋₅alkyl, -OC(O)C₂₋₅alkenyl, -OC(O)C₂₋₅alkynyl, Ar, -OAr, -C(O)Ar, -C(O)OAr, -OC(O)Ar, C₃₋₈Cycloalkyl, -OC₃₋₈Cycloalkyl, -SO_xC₁₋₅alkyl, -SO_xNR^aR^b, -SO_xAr, and -C(O)NR^aR^b, wherein in each instance, each alkyl, alkenyl, and alkynyl is linear or branched and is optionally substituted with (a) 1-5 halogen atoms, (b) 1-2 groups independently selected from -OC₁₋₃alkyl groups which are linear or branched and are optionally substituted with 1-5 halogens, (c) 1 group Ar or C₃₋₆Cycloalkyl, or (d) a mixture of more than one of (a), (b) and (c);

10 R⁴ is selected from the group consisting of Benzoheterocycle, C₃₋₈Cycloalkyl, Hetcyc, -OC₃₋₈Cycloalkyl and R^c, with the proviso that if R⁴ is R^c, then either (1) R¹ is not H, and no more than one of R², R⁶, and R¹⁰ is alkyl, or (2) R² is Cl, Br or F, and R¹⁰ is not alkyl;

15 wherein Benzoheterocycle, C₃₋₈Cycloalkyl, Hetcyc and -OC₃₋₈Cycloalkyl are each optionally substituted with 1-3 groups independently selected from halogen, C₁₋₅alkyl, C₂₋₅alkenyl, C₂₋₅alkynyl, -OC₁₋₅alkyl, -OC₂₋₅alkenyl, -OC₂₋₅alkynyl, C₃₋₈Cycloalkyl, -SO_xC₁₋₅alkyl, -SO_xNR^aR^b, -SO_xphenyl, C(O)C₁₋₃alkyl and -C(O)NR^aR^b, wherein in all instances, said C₁₋₅alkyl, C₂₋₅alkenyl, and C₂₋₅alkynyl groups are linear or branched and are optionally substituted with 1-3 halogens, and wherein Hetcyc, -OC₃₋₈Cycloalkyl and C₃₋₈Cycloalkyl may optionally have a C₃₋₆-spiro-cycloalkyl substituent on the ring where gem-disubstitution of a ring carbon is possible, wherein the spiro-cycloalkyl group is optionally substituted with 1-2 groups independently selected from methyl, trifluoromethyl, methoxy, trifluoromethoxy and halogen;

20 wherein R^c is selected from the group consisting of halogen, -OH, -OSO₂C₁₋₈alkyl, -OSO₂C₃₋₈Cycloalkyl, -OSO₂Ar, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, -OC₁₋₈alkyl, -OC₂₋₈alkenyl, -OC₂₋₈alkynyl, and Aryl, wherein said -OSO₂C₁₋₈alkyl, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, -OC₁₋₈alkyl, -OC₂₋₈alkenyl, and -OC₂₋₈alkynyl are linear or branched, and are optionally substituted with (a) 1-5 halogens, (b) 1-2 groups independently selected from -OC₁₋₃alkyl, which are linear or branched and which are optionally substituted with 1-5 halogens, (c) 1 group selected from Aryl and C₃₋₈Cycloalkyl, or (d) a mixture of one or more of (a), (b)

and (c), and Aryl and C₃₋₈Cycloalkyl are each optionally substituted as defined under Ar for Aryl and R⁴ for C₃₋₈Cycloalkyl;

5 or alternatively R⁴ and the adjacent substituent R³ or R⁵ may be connected to form a 5- or 6-membered heterocyclic ring that may be saturated, partly unsaturated or aromatic fused to the benzene ring, wherein the 5- or 6-membered fused ring comprises 1-3 heteroatoms independently selected from O, S, and N, where N may optionally be NR^A and S may optionally be SO or SO₂, said fused ring optionally also comprising 1-2 C=O groups in the perimeter of the ring, wherein
10 said 5- or 6-membered heterocyclic fused ring is optionally substituted with 1-2 groups independently selected from R³.

15 2. A compound having formula I as recited in Claim 1, wherein X and Y are each O or S.

3. A compound having formula I as recited in Claim 1, wherein X and Y are O.

20 4. A compound having formula I as recited in Claim 1, wherein Z is CH₂.

5. A compound having formula I as recited in Claim 1, wherein Z is C=O.

25 6. A compound having formula I as recited in Claim 1, wherein n is 3 or 4.

30 7. A compound having formula I as recited in Claim 1, wherein R¹ is selected from the group consisting of Cl, Br, F and C₁₋₄ alkyl, wherein said C₁₋₄alkyl is linear or branched and is optionally substituted with 1-3 halogens independently selected from F and Cl, 1 phenyl which is optionally substituted with 1-3 halogens, or a mixture thereof.

8. A compound having formula I as recited in Claim 1, wherein R² is selected from the group consisting of Cl, Br, F and C₁₋₄alkyl, wherein said C₁₋₄alkyl is optionally substituted with 1-3 halogens.

5 9. A compound having formula I as recited in Claim 1, wherein the group -X- is attached to the benzopyran ring at the 6-position of the benzopyran ring.

10 10. A compound having formula I as recited in Claim 1, wherein the group -X- is attached to the benzopyran ring at the 7-position of the benzopyran ring.

15 11. A compound having formula I as recited in Claim 1, wherein R¹ is selected from a group consisting of C₁₋₄alkyl, Cl and F, wherein alkyl is linear or branched and is optionally substituted with 1-5 F.

20 12. A compound as recited in claim 1, wherein Ar is phenyl, which is optionally substituted with 1-4 groups independently selected from Cl, F, C₁₋₅alkyl, -OCH₃, -OCF₃, -SO_xC₁₋₅alkyl, -SO_xNR_aR_b, -SO_xphenyl, -C(O)C₁₋₃alkyl, and -C(O)NR_aR_b, wherein phenyl of -SO_xphenyl is optionally substituted with 1-3 substituents independently selected from halogen, CH₃, CF₃, -OCF₃, and -OCH₃, and wherein alkyl in all occurrences is linear or branched and is optionally substituted with 1-5 halogens.

25 13. A compound as recited in claim 1, wherein R¹ and R² are each independently selected from a group consisting of C₁₋₄alkyl, Cl and F; n is 2-4; X and Y are O; Z is CH₂; R³, R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are independently selected from H, Cl, F, CH₃ and CF₃; and in all occurrences, alkyl is linear or branched and is optionally substituted with 1-5 F.

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14. A compound having formula I as recited in any one of Claims 1-13, wherein R³, R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are H; R² is Cl or F; and R¹ is C₁₋₄alkyl, Cl or F, where C₁₋₄alkyl is linear or branched and is optionally substituted with 1-5 F.

15. A compound having formula I as recited in Claim 1, wherein R³, R⁵ and R⁶ are H.

5 16. A compound as recited in Claim 1, wherein R^a and R^b are independently selected from the group consisting of H, C₁₋₅alkyl, -C(O)C₁₋₅alkyl, S(O)_xC₁₋₅alkyl, S(O)_xphenyl, and phenyl, wherein alkyl in all occurrences is linear or branched and is optionally substituted with 1-5 halogen atoms, and wherein phenyl
10 in all occurrences is optionally substituted with 1-3 substituents independently selected from halogen, C₁₋₃alkyl, and C₁₋₃alkoxy, wherein C₁₋₃alkyl and C₁₋₃alkoxy are linear or branched and are optionally substituted with 1-5 halogens.

17. A compound as recited in Claim 1, wherein R¹ is not H or -CR¹¹R¹²-, and no more than one of R², R⁶, and R¹⁰ is alkyl.

18. A compound as recited in Claim 1, wherein R² is Cl, Br or F, and R¹⁰ is not alkyl.

19. A compound having Formula I as recited in Claim 1, wherein
20 R⁴ is joined to R³ or to R⁵ to yield a benzoheterocycle which comprises a 5 or 6-membered heterocyclic ring which may be saturated, partly unsaturated or aromatic fused to the benzene ring, wherein said benzoheterocycle is selected from the group consisting of benzoxazole, benzisoxazole, benzofuran, indole, benzothiophene, benzthiazole, benzodiazene, quinazoline, benzoxazine, benzisoxazine, benzimidazole,
25 and benzpyrazole, wherein said benzoheterocycle is optionally substituted on the heterocyclic ring with 1-2 groups independently selected from halogen, phenyl, C₁₋₄alkyl, and -OC₁₋₄alkyl, wherein C₁₋₄alkyl and -OC₁₋₄alkyl are linear or branched and are optionally substituted with 1-5 halogens, and said phenyl is optionally substituted with 1-5 substituents independently selected from halogen, C₁₋₃alkyl and C₁₋₃alkoxy groups, wherein the C₁₋₃alkyl and C₁₋₃alkoxy groups are
30 linear or branched and are optionally substituted with 1-5 halogens.

20. A compound having formula I as recited in Claim 19, wherein R⁴ and R³ or R⁵ are joined together to form a benzisoxazole ring, which is optionally
35 substituted on the isoxazole ring with 1 group selected from C₁₋₄alkyl and phenyl,

wherein C₁₋₄alkyl is linear or branched and is optionally substituted with (a) 1-3 halogens, (b) 1 phenyl, or (c) a mixture of (a) and (b); and phenyl in all occurrences is optionally substituted with 1-3 groups independently selected from halogen, C₁₋₃alkyl and -OC₁₋₃alkyl, wherein said C₁₋₃alkyl and -OC₁₋₃alkyl are linear or branched and are optionally substituted with 1-3 halogens.

21. A compound having Formula I as recited in Claim 1, wherein R⁴ is selected from the group consisting of C₃₋₈Cycloalkyl and Hetcyc, each of which is optionally substituted with 1-4 substituents independently selected from halogen, phenyl, C₁₋₅alkyl, and -OC₁₋₅alkyl, wherein C₁₋₅alkyl and -OC₁₋₅alkyl are linear or branched and are optionally substituted with 1-5 halogens, and phenyl is optionally substituted with 1-5 substituents independently selected from halogen, C₁₋₃alkyl and -OC₁₋₃alkyl, wherein C₁₋₃alkyl and -OC₁₋₃alkyl are linear or branched and are optionally substituted with 1-5 halogens, and wherein two substituents on the same carbon of said C₃₋₈Cycloalkyl and Hetcyc may optionally join together to form a C₃₋₆-spiro-cycloalkyl group, wherein the spiro-cycloalkyl group is optionally substituted with 1-2 groups independently selected from methyl, trifluoromethyl, methoxy, trifluoromethoxy and halogen.

22. A compound having Formula I as recited in Claim 21, wherein R⁴ is Hetcyc or C₃₋₆Cycloalkyl, wherein Hetcyc is a saturated heterocyclic compound having 1-2 heteroatoms in the perimeter of the ring and is otherwise as defined in Claim 1, and C₃₋₆Cycloalkyl is a saturated 3-6-membered cycloalkyl, wherein Hetcyc and C₃₋₆Cycloalkyl optionally have 1-2 substituents independently selected from halogen, C₁₋₃alkyl and C₂₋₃alkenyl, wherein said C₁₋₃alkyl and C₂₋₃alkenyl are linear or branched and are optionally substituted with 1-3 halogens, or alternatively two substituents may be joined on one carbon atom of the ring to form a spiro-cycloalkyl group having 3-6 carbons.

23. A compound having formula I as recited in Claim 22, wherein R⁴ is selected from piperidine, 1,4-dioxane, tetrahydropyran, piperazine, morpholine,

cyclohexane, cyclopentane, cyclobutane and cyclopropane, wherein R⁴ is optionally substituted as defined in Claim 22.

24. A compound having formula I as recited in Claim 23, wherein
- 5 R⁴ is R^C and is selected from the group consisting of halogen, C₁-8alkyl, C₂-8alkenyl, C₂-8alkynyl, -OC₁-8alkyl, -OC₂-8alkenyl, -OC₂-8alkynyl, and Aryl, wherein C₁-8alkyl, C₂-8alkenyl, C₂-8alkynyl, -OC₁-8alkyl, -OC₂-8alkenyl, and -OC₂-8alkynyl are linear or branched, and are optionally substituted with (a) 1-5
- 10 halogens, (b) 1-2 groups independently selected from -OC₁-3alkyl, which are linear or branched and which are optionally substituted with 1-5 halogens, (c) 1 group Aryl or C₃-8Cycloalkyl, or (d) a mixture of more than one of (a), (b) and (c), wherein Aryl and C₃-8Cycloalkyl are optionally substituted with 1-3 substituents independently selected from halogen, C₁-3alkyl and -OC₁-3alkyl, said C₁-3alkyl and -OC₁-3alkyl
- 15 being linear or branched and optionally substituted with 1-5 halogens, phenyl or C₃-6Cycloalkyl.

25. A compound having formula I as recited in Claim 24, wherein
- R⁴ is selected from the group consisting of C₁-4alkyl and -OC₁-4alkyl, wherein said C₁-4alkyl and -OC₁-4alkyl are linear or branched and are optionally substituted with
- 20 one C₃-6Cycloalkyl group, 1-5 halogens independently selected from Cl and F, or a mixture of both.

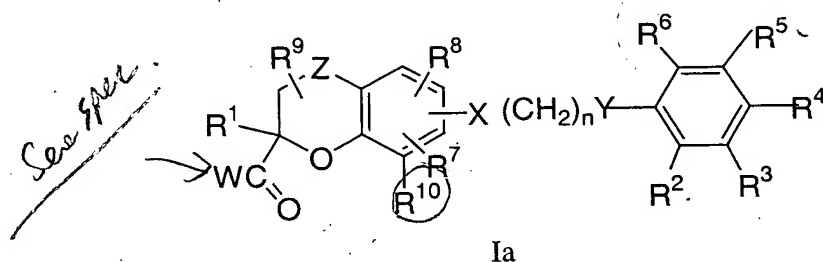
26. A compound having formula I as recited in Claim 24, wherein
- Aryl is phenyl; R¹ is selected from a group consisting of C₁-4alkyl, Cl and F, wherein
- 25 alkyl is linear or branched and is optionally substituted with 1-5 F; R² is selected from Cl and F; and R³, R⁵, R⁶, R⁷, R⁸, R⁹, and R¹⁰ are independently selected from H, CH₃, CF₃, Cl and F.

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H3
27. A compound having formula I as recited in any one of Claims 1-26, wherein R³, R⁵, R⁶, R⁷, R⁸, R⁹, and R¹⁰ are H; R¹ is C₁-4alkyl, Cl or F; and R² is Cl or F.

28. A compound having formula I as recited in Claim 1, wherein
- R¹ is selected from linear or branched C₁-4 alkyl, Cl and F; R² is Cl or F; R³, R⁵,

- R⁶, R⁷, R⁸, R⁹ and R¹⁰ are each H; Z is CH₂; X and Y are O or S; and R⁴ is selected from halogen, phenyl, C₁-alkyl, -OC₁-alkyl, C₃-6Cycloalkyl, and tetrahydropyran, wherein said C₁-alkyl and -OC₁-alkyl groups are linear or branched and are optionally substituted with (a) 1-5 halogen atoms, (b) 1 group selected from phenyl, C₃-6Cycloalkyl, and linear or branched -OC₁-3alkyl optionally substituted with 1-5 halogens, or (c) a mixture of (a) and (b), and wherein said phenyl, C₃-6Cycloalkyl and tetrahydropyran groups are optionally substituted with 1-2 groups independently selected from halogen, -OCH₃, -CH₃, -OCF₃, and -CF₃.

29. A compound having formula Ia:



or a pharmaceutically acceptable salt or metabolite thereof, wherein W is a group that is easily removed under physiological conditions during or after administration to a mammalian patient to yield a carboxylic acid in which W is OH, or the carboxylate anion thereof, or a pharmaceutically acceptable salt thereof, and R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², Ar, X, Y, Z, R^a, R^b, R^d, R^e, x and n are as defined in Claim 1.

30. A compound as recited in Claim 29, wherein W is selected from the group consisting of -OR¹³, -OCH₂OR¹³, -OCH(CH₃)OR¹³, -OCH₂OC(O)R¹³, -OCH(CH₃)OC(O)R¹³, -OCH₂OC(O)OR¹³, -OCH(CH₃)OC(O)OR¹³, and -NR¹⁴R¹⁴, wherein each R¹³ is independently selected from C₁-C₆ alkyl optionally substituted with one or two groups independently selected from -CO₂H, -CONH₂, NH₂, -OH, -OAc, NHAc and phenyl; and wherein each R¹⁴ is independently selected from H and R¹³.

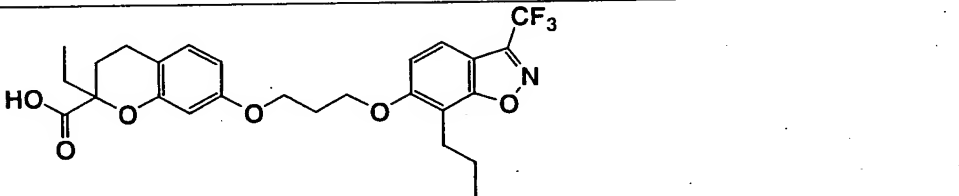
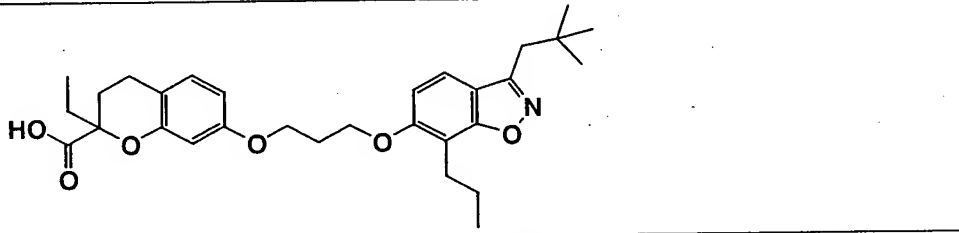
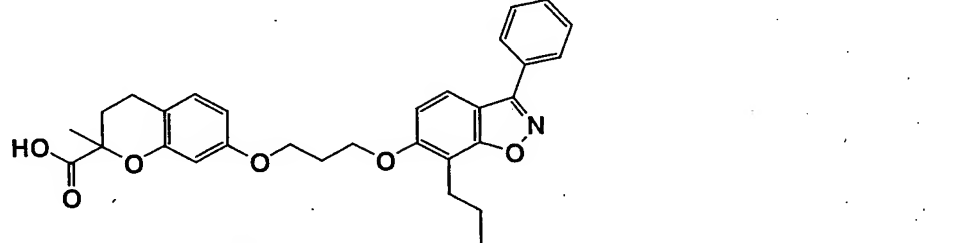
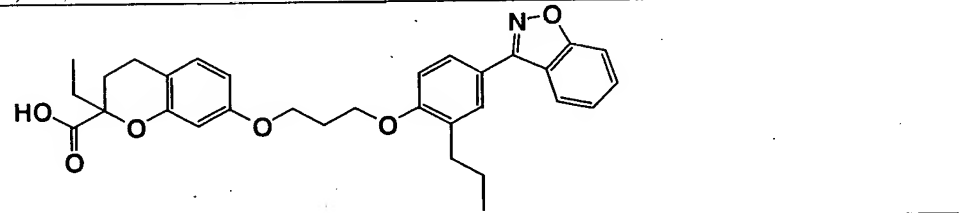
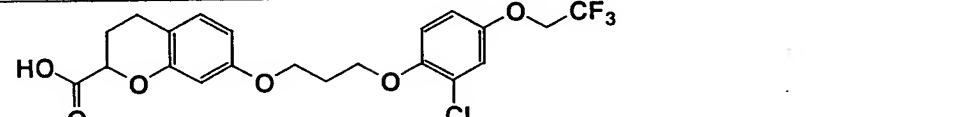
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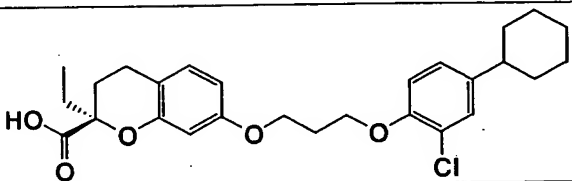
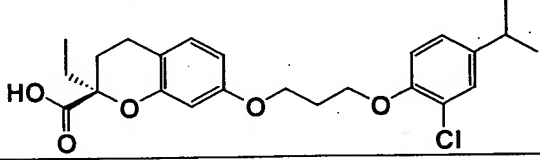
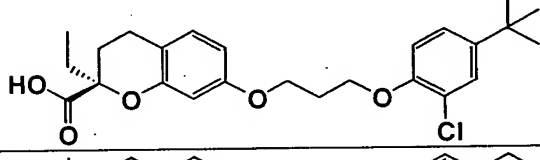
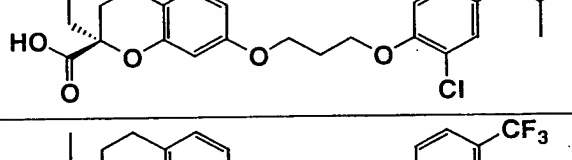
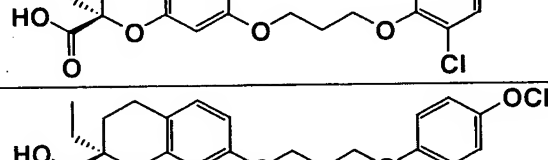
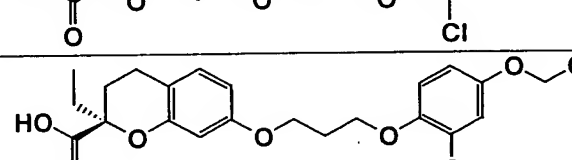
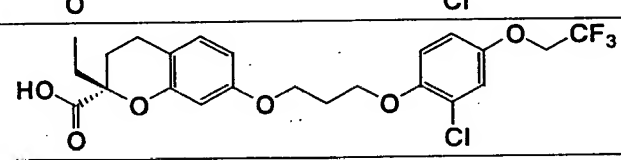
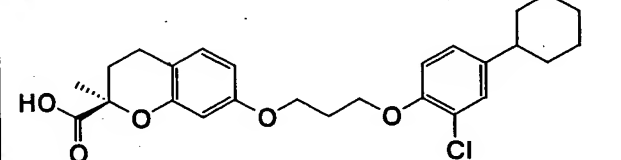
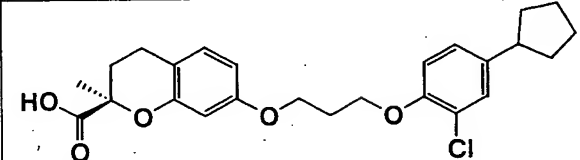

31. A compound as recited in any one of Claims 1-30, wherein the stereochemistry at the 2-position of the benzopyranyl ring is R.
32. A compound as recited in any one of Claims 1-30, wherein the stereochemistry at the 2-position of the benzopyranyl ring is S.

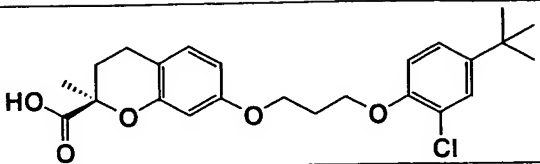
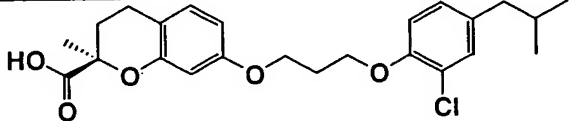
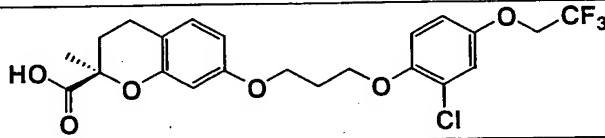
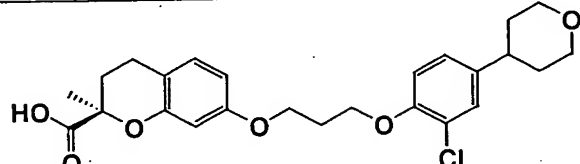
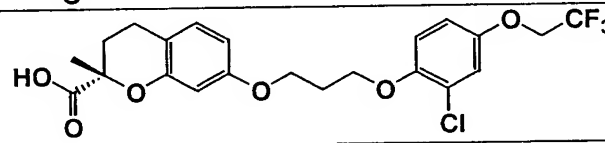
33. A compound represented by any of the structures of Examples 1- 29, shown below, or a pharmaceutically acceptable salt or prodrug thereof:

formulas

10

	Example 1
	Example 2
	Example 3
	Example 4
	Example 5

	Example 15
	Example 16
	Example 17
	Example 18
	Example 19
	Example 20
	Example 21
	Example 22
	Example 23
	Example 24

	Example 25
	Example 26
	Example 27
	Example 28
	Example 29

34. A compound according to Claim 1, selected from the list of compounds below, or a pharmaceutically acceptable salt or prodrug thereof:

Example 1: 7-(3-(3-Trifluoromethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propoxy)-2-ethylchromane-2-carboxylic acid;

Example 2: 7-(3-(3-(2,2-Dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propoxy)-2-ethylchromane-2-carboxylic acid;

Example 3: 7-(3-(3-Phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propoxy)-2-methylchromane-2-carboxylic acid;

Example 4: 7-(3-(4-(1,2-Benzisoxazol-3-yl)-2-propylphenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

Example 5: 7-(3-(2-Chloro-4-(2,2,2-trifluoroethoxy)phenoxy)propoxy)-chromane-2-carboxylic acid;

5 Example 6: 7-(3-(2-Chloro-4-(2,2,2-trifluoroethoxy)phenoxy)propoxy)-2-methylchromane-2-carboxylic acid;

Example 7: 7-(3-(2-Chloro-4-(2,2,2-trifluoroethoxy)phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

10 Example 8: 7-(3-(2-Chloro-4-(2,2,2-trifluoroethoxy)phenoxy)propoxy)-2-propylchromane-2-carboxylic acid;

Example 9: 7-(3-(2-Propyl-4-(2,2,2-trifluoroethoxy)phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

15 Example 10: 7-(3-(2-Chloro-4-tert-butylphenoxy)propoxy)-2-methylchromane-2-carboxylic acid;

20 Example 11: 7-(3-(2-Chloro-4-cyclohexylphenoxy)propoxy)-2-methylchromane-2-carboxylic acid;

Example 12: 7-(3-(2-Chloro-4-cyclohexylphenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

25 Example 13: (2R)-7-(3-(2-Chloro-4-(4-tetrahydropyranyl)phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

Example 14: (2R)-7-(3-(2-Chloro-4-(4,4-dimethylcyclohexyl)phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

30

Example 15: (2R)-7-(3-(2-Chloro-4-cyclohexylphenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

Example 16: (2R)-7-(3-(2-Chloro-4-isopropylphenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

5 Example 17: (2R)-7-(3-(2-Chloro-4-tert-butylphenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

Example 18: (2R)-7-(3-(2-Chloro-4-isobutylphenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

10 Example 19: (2R)-7-(3-(2-Chloro-4-trifluoromethylphenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

Example 20: (2R)-7-(3-(2-Chloro-4-trifluoromethoxyphenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

15 Example 21: (2R)-7-(3-(2-Chloro-4-(2,2,2-trifluoroethoxy)phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

20 Example 22: (2S)-7-(3-(2-Chloro-4-(2,2,2-trifluoroethoxy)phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

Example 23: (2R)-7-(3-(2-Chloro-4-cyclohexylphenoxy)propoxy)-2-methylchromane-2-carboxylic acid;

25 Example 24: (2R)-7-(3-(2-Chloro-4-cyclopentylphenoxy)propoxy)-2-methylchromane-2-carboxylic acid;

Example 25: (2R)-7-(3-(2-Chloro-4-tert-butylphenoxy)propoxy)-2-methylchromane-2-carboxylic acid;

30 Example 26: (2R)-7-(3-(2-Chloro-4-isobutylphenoxy)propoxy)-2-methylchromane-2-carboxylic acid;

Example 27: (2R)-7-(3-(2-Chloro-4-(2,2,2-trifluoroethoxy)phenoxy)propoxy)-2-methylchromane-2-carboxylic acid;

Example 28: (2R)-7-(3-(2-Chloro-4-(4-tetrahydropyranyl)phenoxy)propoxy)-2-methylchromane-2-carboxylic acid; and

- 5 Example 29: (2S)-7-(3-(2-Chloro-4-(2,2,2-trifluoroethoxy)phenoxy)propoxy)-2-methylchromane-2-carboxylic acid.

35. A pharmaceutical composition comprising a compound as identified in any of Claims 1-34 and a pharmaceutically acceptable carrier.

36. A method for treating, controlling, or preventing non-insulin dependent (Type 2) diabetes mellitus in a mammalian patient in need of such treatment which comprises administering to said patient a therapeutically effective amount of a compound of Claim 1.

37. A method for treating, controlling or preventing hyperglycemia in a mammalian patient in need of such treatment which comprises administering to said patient a therapeutically effective amount of a compound of Claim 1.

38. A method for treating, controlling or preventing lipid disorders, hyperlipidemia, or low HDL in a mammalian patient in need of such treatment which comprises administering to said patient a therapeutically effective amount of a compound of Claim 1.

39. A method for treating, controlling or preventing obesity in a mammalian patient in need of such treatment which comprises administering to said patient a therapeutically effective amount of a compound of Claim 1.

40. A method for treating, controlling or preventing hypercholesterolemia in a mammalian patient in need of such treatment which comprises administering to said patient a therapeutically effective amount of a compound of Claim 1.

41. A method for treating, controlling or preventing hypertriglyceridemia in a mammalian patient in need of such treatment which

42. A method for treating, controlling or preventing dyslipidemia and/or low HDL cholesterol in a mammalian patient in need of such treatment which comprises administering to said patient a therapeutically effective amount of a compound of Claim 1.

44. A method for treating, controlling or preventing cachexia in a mammalian patient in need of such treatment which comprises administering to said patient a therapeutically effective amount of a compound of Claim 1.

↳ to what?

46. A method of treating, controlling or preventing one or more diseases, disorders, or conditions selected from the group consisting of (1) diabetes mellitus, and especially non-insulin dependent diabetes mellitus (NIDDM), (2) hyperglycemia, (3) impaired glucose tolerance, (4) insulin resistance, (5) obesity, (6) lipid disorders, (7) dyslipidemia, (8) hyperlipidemia, (9) hypertriglyceridemia, (10) hypercholesterolemia, (11) low HDL levels, (12) high LDL levels, (13) atherosclerosis and its sequelae, (14) vascular restenosis, (15) irritable bowel syndrome, (16) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (17) other inflammatory conditions, (18) pancreatitis, (19) abdominal obesity, (20) neurodegenerative disease, (21) retinopathy, (22) neoplastic conditions, (23) adipose cell tumors, (24) adipose cell carcinomas, such as liposarcoma, (25) prostate cancer and other cancers, including gastric, breast, bladder and colon cancers, (26) angiogenesis, (27) Alzheimer's disease, (28) psoriasis, (29) acne vulgaris, (30) skin diseases modulated by PPAR, (31) high blood pressure, (32) Syndrome X, (33) ovarian hyperandrogenism (polycystic ovarian syndrome), and other disorders where insulin resistance is a component, said method comprising the administration of an effective amount of a compound of Claim 1, and an effective amount of one or more other compounds selected from the group consisting of:

- (a) insulin sensitizers including (i) PPAR γ agonists such as the glitazones (e.g. troglitazone, pioglitazone, englitazone, MCC-555, rosiglitazone, and the-like), and compounds disclosed in WO97/27857, 97/28115, 97/28137 and 97/27847; (ii) biguanides such as metformin and phenformin; (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors, and (iv) dipeptidyl peptidase IV inhibitors;
- (b) insulin or insulin mimetics;
- (c) sulfonylureas such as tolbutamide and glipizide, or related materials;
- (d) α -glucosidase inhibitors (such as acarbose);
- (e) cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, ZD-4522 and other statins), (ii) sequestrants (cholestyramine, colestipol, and dialkylaminoalkyl derivatives of a cross-linked dextran), (iii) nicotinic alcohol, nicotinic acid or a salt thereof, (iv) PPAR α agonists such as fibric acid derivatives (clofibrate, fenofibrate and bezafibrate) or gemfibrozil, (v) PPAR α/γ dual agonists, such as KRP-297, (vi) inhibitors of cholesterol absorption, such as for example

51. A method for treating, preventing or controlling atherosclerosis in a mammalian patient in need of such treatment comprising the administration to said patient of an effective amount of a compound of Claim 1 and an effective amount of an HMG-CoA reductase inhibitor.

52. The method as recited in Claim 51, wherein the HMG-CoA reductase inhibitor is a statin.

5 53. The method as recited in Claim 52, wherein the statin is selected from the group consisting of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, itavastatin, ZD-4522 and rivastatin.

10 54. A pharmaceutical composition for the treatment, prevention or control of atherosclerosis, comprising: (1) a compound according to Claim 1, (2) an HMG-CoA reductase inhibitor, and (3) a pharmaceutically acceptable carrier.

15 55. A pharmaceutical composition comprising (1) a compound according to Claim 1, (2) one or more compounds selected from the group consisting of:

20 (a) insulin sensitizers including (i) PPAR γ agonists such as the glitazones (e.g. troglitazone, pioglitazone, englitazone, MCC-555, rosiglitazone, and the like), and compounds disclosed in WO97/27857, 97/28115, 97/28137 and 97/27847; (ii) biguanides such as metformin and phenformin; (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors, and (iv) dipeptidyl peptidase IV (DP-IV) inhibitors;

(b) insulin or insulin mimetics;
(c) sulfonylureas such as tolbutamide and glipizide, or related materials;

25 (d) α -glucosidase inhibitors (such as acarbose);
(e) cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, ZD-4522 and other statins), (ii) sequestrants (cholestyramine, colestipol, and dialkylaminoalkyl derivatives of a cross-linked dextran), (iii) nicotiny alcohol, 30 nicotinic acid or a salt thereof, (iv) PPAR α agonists such as fibric acid derivatives (clofibrate, fenofibrate and bezafibrate) or gemfibrozil, (v) PPAR α/γ dual agonists, such as KRP-297, (vi) inhibitors of cholesterol absorption, such as for example ezetimibe, (vii) acyl CoA:cholesterol acyltransferase inhibitors, such as for example avasimibe, and (viii) anti-oxidants, such as probucol;

35 (f) PPAR δ agonists such as those disclosed in WO97/28149;

(g) antiobesity compounds (anorectics) such as fenfluramine, dexfenfluramine, phentermine, sibutramine, mazindol, orlistat, lipase inhibitors, neuropeptide Y5 inhibitors, and β_3 adrenergic receptor agonists;

(h) an ileal bile acid transporter inhibitor; and

(i) agents intended for use in inflammatory conditions such as aspirin, non-steroidal anti-inflammatory drugs, glucocorticoids, azulfidine, and cyclo-oxygenase 2 selective inhibitors; and

(3) a pharmaceutically acceptable carrier.

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